

Application No. 10/627,483
 Reply to Office Action of March 30, 2005

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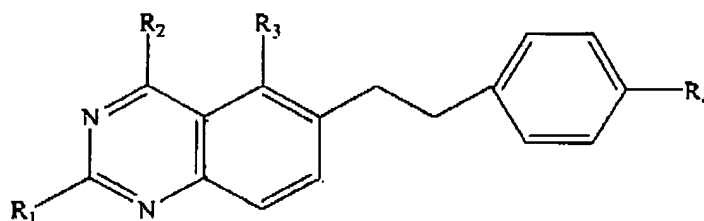
Amendments to and Listing of the Claims:

Please amend the claims as set forth in the following listing of claims, which replaces all prior claim listings:

1. and 2. (Canceled)

3. (Currently Amended) In a process for synthesizing a compound of formula Ib:

(Ib)



wherein R_1 and R_2 are each individually amino or N-alkyl substituted amino; hydroxy; alkoxy; keto; lower alkyl; ~~or a nitrogen or oxygen protecting group;~~

R_3 is hydrogen; hydroxy; alkoxy; trifluoromethyl alkoxy; halo; sulfhydryl or alkylthio;

R_4 is $-C(O)-X$;

X is ~~hydroxy;~~ alkoxy; or γ -methylene glutamic acid, glutamic acid, aspartic acid, or γ -methylene glutamate ~~an amino acid residue;~~

in which process a 2-amino-5-nitro-benzonitrile starting reagent is cyclized to form 2,4-diamino-6-nitro-quinazoline, which is converted to 2,4,6-triamino-quinazoline, which is converted to 2,4-diamino-6-cyano-quinazoline, which is converted to 2,4-diamino-6-formyl-quinazoline;

the improvement comprising:

reacting a ~~bromo-alkyl~~ an R_4 - p -benzoic acid alkylene moiety with triethyl phosphite to form a 4- R_4 -carbonyloxyalkyl-phenyl-alkyldiethylphosphite~~onate~~; and

reacting the 2,4-diamino-6-formyl-quinazoline with the 4- R_4 -carbonyloxyalkyl-phenyl-alkyldiethylphosphite~~onate~~ to form a product with an unsaturated bond; and ~~to form the compound of formula Ib.~~

reducing said product to form the compound of formula Ib.

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4. (Currently Amended) The process of claim 3, wherein the product with an unsaturated bond an ~~R₄-p-benzoic acid~~ alkylene moiety is a methylene moiety.

5. (Currently Amended) The process of claim 4, wherein the ~~R₄-p-benzoic acid~~ methylene moiety is 4-(~~bromo~~ 1,2-methylene)benzoate.

6. (canceled)

7. (canceled)

8. (Currently Amended) The process of claim 3, wherein the 4-R₄-carbonyloxyalkyl-phenyl-alkyldiethylphosphiteonate is 4-carbonyloxymethyl-phenyl-methyldiethylphosphiteonate.

9. (previously presented) The process of claim 3, further comprising hydrogenating the compound of formula Ib to form 6-(4-R₄-carbonyloxyalkylphenyl)ethanyl-2,5-diamino quinazoline, which is hydrolyzed to form 6-(4-R₄-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline,

the improvement further comprising:

reacting 6-(4-R₄-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline with diethyl γ -methylene-L-glutamate to form γ -methylene glutamate 5,8,10-trideaza aminopterin diethyl ester.

10. (previously presented) The process of claim 9, wherein the improvement further comprises reacting the 6-(4-R₄-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline with the diethyl γ -methylene-L-glutamate in the presence of 1-hydroxy benzotriazole and 1-[3-dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride.

11. (previously presented) The process of claim 9, wherein the improvement further comprises reacting the 6-(4-R₄-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline with the diethyl γ -methylene-L-glutamate in the presence of 1-hydroxy benzotriazole, 1-[3-dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride and triethylamine.